

Review**Myocardial Infarction in the Elderly****Amelia Carro, Juan Carlos Kaski***

Cardiovascular Sciences Research Centre, Division of Clinical Sciences, St George's University of London, London, United Kingdom

[Received December 6, 2010; Revised December 21, 2010; Accepted December 21, 2010]

ABSTRACT: Advances in pharmacological treatment and effective early myocardial revascularization have –in recent years- led to improved clinical outcomes in patients with acute myocardial infarction (AMI). However, it has been suggested that compared to younger subjects, elderly AMI patients are less likely to receive evidence-based treatment, including myocardial revascularization therapy. Several reasons have been postulated to explain this trend, including uncertainty regarding the true benefits of the interventions commonly used in this setting as well as increased risk mainly associated with comorbidities. The diagnosis, management, and post-hospitalization care of elderly patients presenting with an acute coronary syndrome pose many difficulties at present. A complex interplay of variables such as comorbidities, functional and socioeconomic status, side effects associated with multiple drug administration, and individual biologic variability, all contribute to creating a complex clinical scenario. In this complex setting, clinicians are often required to extrapolate evidence-based results obtained in cardiovascular trials from which older patients are often, implicitly or explicitly, excluded. This article reviews current recommendations regarding management of AMI in the elderly.

Key words: Management of elderly patients; acute myocardial infarction; age; myocardial reperfusion

Cardiovascular heart disease represents the leading cause of death in both men and women older than 65 years [1-3]. The prevalence and the severity of atherosclerotic coronary artery disease (CAD) increase with age in both men and women. Autopsy studies have shown that more than 50% of the people older than 60 years have significant CAD, with increasing prevalence of left main and/or triple-vessel CAD with older age [4]. Subclinical vascular disease, i.e. abnormal echocardiograms, increased carotid intima-media thickness or an abnormal ankle brachial index, is common in elderly people with electrocardiographic (ECG) evidence of myocardial infarction (MI). In the Cardiovascular Health Study, such abnormalities were detected in 22 percent of women and 33 percent of men aged 65 to 70 years and 43 percent of women and 45 percent of men older than 85 years (Figure 1) [5, 6]. The lifetime risk of developing symptomatic CAD is estimated as 1 in 3 for men and 1 in 4 for women, with onset of symptoms about 10 years earlier in men than women

and with hypertension, diabetes, and lipid abnormalities influencing individual risk [7]. In 2 large registries that collectively enrolled 69,000 acute coronary syndrome (ACS) patients, 32% [8] and 35% [9] of the patients were ≥ 75 years old. However, older patients are generally underrepresented in trials [10]. Participation of elderly patients in ACS trials has not increased over the 1970-2000 period, compared to previous years, despite the fact that this population has continued to expand [11-14].

The absence of reliable data regarding elderly patients often results in these high-risk individuals being subjected to more conservative treatment strategies, which at times diverge significantly from recommendations in accepted guidelines. This article addresses some of the clinical issues that affect optimal care of elderly patients with persistent ST segment elevation MI (STEMI) and highlights findings in recent studies that provide new insights into the complex area of cardiovascular care in the elderly.

*Correspondence should be addressed to: Juan Carlos Kaski MD, DSc; St George's University of London, Cardiovascular Biology Research Centre, Division of Cardiac and Vascular Sciences; Cranmer Terrace, London SW17 0RE, United Kingdom; E-mail: jkaski@sgul.ac.uk
ISSN: 2152-5250

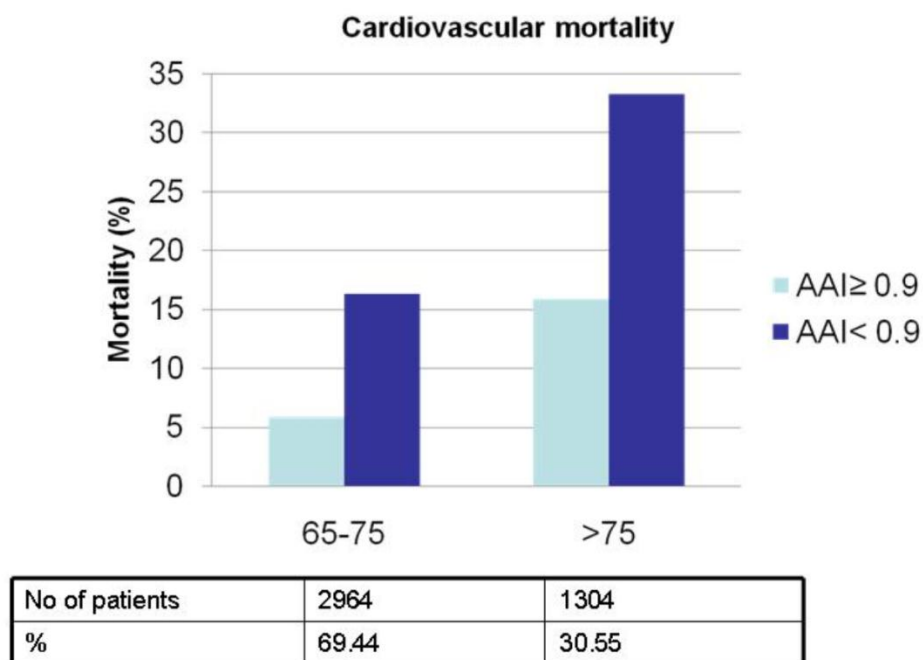


Figure 1: CV mortality in Cardiovascular Heart Study participants without CVD at baseline. Older people (>75) represented one third of the population, but had a significantly higher cardiovascular mortality (RR 1.12; 95%CI: 1.08, 1.17) when compared to the group aged 65-75. AAI was also an independent predictor of CV mortality (RR 2.03; 95%CI: 1.22, 3.37)

CLINICAL PRESENTATION

Although the absolute number of patients with STEMI increases with age, STEMI accounts for a smaller proportion of all ACS admissions in older subgroups (<30% ≥ 75 years of age) [9].

Clinical profile

Presenting symptoms of acute MI differ in the elderly from those in younger patients. They are more likely to be termed “atypical” because the description differs from the classical one of subesternal pressure with exertion [15]. When pain is the presenting complaint, it may be different in character or location, and sometimes appears as an upper abdomen pain rather than a crushing or squeezing subesternal sensation. Elderly patients have changes in pain perception and altered ischemic thresholds [16], but the exact explanation for atypical pain syndromes is not known. In the National Registry of Myocardial infarction (NRFI), chest pain at presentation occurred in 89.9% of STEMI patients <65 years versus 56.8% of those

≥ 85 years of age [17]. In the Worcester Heart Attack Study, chest pain was reported in 63% of the overall population, but was reported in less than half of the women over age 75 years (45.5%) [18].

Symptoms may be described primarily as dyspnea, syncope, shoulder or back pain, weakness, fatigue (in women), acute confusion, epicardial discomfort and may be precipitated by concurrent illnesses [19]. Age related changes, comorbidities and other mechanisms had been suggested for these particular presentations (Table 1). However, complications derived from MI may be the only presenting sign. In the NRFI registry, acute heart failure as evidenced by Killip class ≥ 2 at presentation occurred in 11.7% of STEMI patients <65 years versus nearly half (44.6%) of those ≥ 85 years of age [17]. The common occurrence of heart failure and atypical symptoms in older patients may divert diagnostic suspicion away from an acute ischemic event. Accordingly, a diagnosis of “other” (as opposed to unstable angina, rule-out MI, or MI) was more often recorded at admission in older adults (5% of those <65 versus 24% of those ≥ 85 years of age) [17].

Table 1. Pathophysiology of atypical STEMI presentations in the elderly

LEADING SYMPTOM	PROPOSED MECHANISMS
Dyspnea	<ul style="list-style-type: none"> •Transient rise in LV pressure during ischemic event •Acute left ventricular systolic dysfunction •Age-dependent pulmonary changes •Associated lung disease
Atypical Symptoms	Comorbid conditions (pain distracters)
Absent/Atypical chest pain	<ul style="list-style-type: none"> •<u>Altered pain perception</u>: <ul style="list-style-type: none"> -Increased level of endogenous opioids -Increased opioid receptor sensitivity -Impaired autonomic peripheral nerve and central mechanisms -Sensory neuropathy •<u>Ischemic preconditioning</u>: <ul style="list-style-type: none"> -Higher prevalence of repetitive episodes of ischemia -Higher prevalence of DM -Higher prevalence of multivessel disease -Higher prevalence of collateral flow •<u>Impaired ability to recall/report symptoms</u>
Neurologic symptoms (Syncope, stroke, acute confusion)	<ul style="list-style-type: none"> •Associated cerebrovascular disease •Acute reduction of central nervous system blood supply •Associated complications (embolism, hemorrhage)

LV: left ventricular. DM: diabetes mellitus

Electrocardiogram

The ECG of older patients may demonstrate a variety of abnormalities which act as important confounders in the ability to electrocardiographically classify these forms of ACS. The occurrence of left bundle branch block (LBBB) in the elderly is higher than in younger population. Among STEMI patients in the NRMI registry, ST-segment elevation was present on the ECG of 96.3% of patients <65 years but only 69.9% of those ≥85 years of age [17]. Conversely, LBBB occurred in 5% of those <65 years but 33.8% of those ≥85 years of age. In the combined NRMI 1, 2 and 3 data set, an increasingly proportion in the prevalence of non-Q wave infarctions was observed (from 45% in 1994 to 63% in 1999, $p=0.0001$) [20]. In addition, elderly people might present preexisting ST-T segment abnormalities that mimic changes related to myocardial ischemia, even in the absence of ACS [21].

Biomarkers

The universal definition of myocardial infarction requires evidence of an increase and decrease in cardiac troponin (cTn) in a clinical setting suggestive of myocardial ischemia with, together with clinical symptoms, new ischemic ECG changes, or imaging

findings of new loss of myocardium [22]. However, troponin may be increased in patients with a variety of chronic cardiac conditions (Table 2) [23-25] and, to a lesser extent, also in apparently healthy persons [26, 27]. Eggers et al. showed that cTnI >99th percentile, in combination with significant ST-T segment abnormalities, were present in 0.6% of 995 subjects >70 years participating in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) Study [28]. Therefore, the detection of a true and significant increase and/or decrease in serially measured troponin is of critical importance to correctly establish the diagnosis of AMI and discriminate ischemic or other acute causes from chronic causes of troponin increase. Clinicians must be aware that troponin elevation can be seen in other conditions than AMI, and that many of these conditions are increasingly prevalent with age (Table 2). Failure to acknowledge the differential diagnosis of elevated troponin not only would lead to over-diagnosis of MI, but it would also misdiagnose the real cause and the lack of its appropriate treatment [29].

Delayed presentation

Prehospital delays are common in older adults, possibly related to diminished chest pain sensation,

Table 2. Etiology of elevated troponin levels in the absence of MI

DISEASE	MECHANISM FOR Tn RELEASE
NON-TRHOMBOTIC CARDIAC TISSUE DAMAGE	
Congestive heart failure	<ul style="list-style-type: none"> • Release of cytokines • Destruction of contractile proteins • LVH • Global wall stretch • Impaired hemodynamic function • Concomitant renal disease
Coronary vasospasm	<ul style="list-style-type: none"> • Reversible/Irreversible tissue damage • Altered transient membrane permeability
Cardiac trauma	<ul style="list-style-type: none"> • Myocyte damage • Altered myocyte integrity • Trauma to coronary arteries
Myocarditis/Perimyocarditis	<ul style="list-style-type: none"> • Troponin spillage from myocardial cell necrosis • Damage of the outermost layer of the myocardium
Pulmonary embolism	<ul style="list-style-type: none"> • Right ventricular dilation • Right ventricular strain
Postcardiac surgery/ablation Cardioversion Cardiopulmonary resuscitation	<ul style="list-style-type: none"> • Prolonged hypotension and hypoxemia • Mechanical and electrical trauma (chest compressions, defibrillation)
Sepsis/critically ill patients	<ul style="list-style-type: none"> • Release of cytokines and reactive oxygen species • Direct effect of bacterial endotoxins • Concomitant myocarditis • Prolonged hypotension • Dysfunction of the coronary autorregulation
End-stage renal disease	<ul style="list-style-type: none"> • Decreased renal elimination • Uremic myo/pericarditis • Congestive heart failure • LVH • Hemoconcentration following dialysis
Arrhythmias (tachycardias, bradycardias)	<ul style="list-style-type: none"> • Hemodynamic compromise • Reversible myocyte injury
Stroke	Neurally mediated myocyte damage
Epileptic seizures	<ul style="list-style-type: none"> • Neurally mediated myocyte damage • Transient supply-demand mismatch secondary to increased afterload by tonic skeletal muscle contraction
FALSE POSITIVE cTn TESTING	
Heterophile antibodies	Interference in several immunoassays, cardiac Tn included
Reumatoid factor	
Macroenzymes	
Circulating antibodies (vaccinations, immunotherapies, blood transfusions)	
Fibrin clots	Analyzer error
Malfunction of the analyzer	

Tn: Troponin. LVH: left ventricular hypertrophy

cognitive impairment, comorbid illness, or social constraints [30]. Atypical symptoms may slow the

patient's own recognition of an acute cardiac event, and are further confounded by socioeconomic and

cognitive factors [30-32]. In the Global Registry of Acute Coronary Events (GRACE) registry, the median time from symptom onset to presentation was 2.3 hours in those under 45 years, but 3.0 hours over age 85 [33]. Those with STEMI were more likely to present promptly than those with non-STEMI (median 2.3 hours versus 3.0 hours). Older and male patients, diabetics, and those with prior angina were more likely to delay, whereas patients with diaphoresis, acute heart failure, severe chest pain, or traveling by ambulance were less likely to delay [34]. In the Cooperative Cardiovascular Project, the predictors of late arrival (>6 hours after symptom onset) included

advanced age (65-74y: OR 1.35 95% CI 0.91, 1.98; ≥75y: OR 1.53 95% CI 0.89, 2.61) and diabetes (OR 1.19 95% CI 1.02, 1.37), whereas experiencing chest pain as the chief complaint predicted early presentation (OR 0.78, 95% CI 0.68, 0.98) [35]. The mean time from symptom onset to presentation in community elderly (≥75 years of age) was notably longer than among the elderly in fibrinolytic trials (4.7 versus 2.1 hours, respectively) [31] [36, 37]. However, even in the latter, older age is associated with delayed presentation as well as the increased risk of adverse in-hospital events [37, 38].

Table 3: Recommendations on STEMI treatments on AHA/ACC [41] and ESC [39] guidelines. Differences between American and European societies.

THERAPY	AHA/ACC GUIDELINES	ESC GUIDELINES
REPERFUSION THERAPY	No age restriction (IA)	No age restriction (IA)
PRIMARY PCI	No age restriction (IA)	No age restriction (IA)
FIBRINOLYSIS	No age restriction (IB)	No age restriction (IA)
ANTIPLATELET CO-THERAPY FOR PCI	<ul style="list-style-type: none"> • ASPIRIN: No age restriction. If already on Aspirin 75-325 mg before PCI (IA). Loading dose (300-325 mg) if not on Aspirin (IC) • THIENOPYRIDINE: No age restriction. Options: <ol style="list-style-type: none"> a. CLOPIDOGREL: 300-600mg (IC) b. PRASUGREL: 60 mg (IB) • ANTI IIbIIIa No age restriction <ol style="list-style-type: none"> a. Abciximab (IIaA) b. Eptifibatide (IIaB) c. Tirofiban (IIaB) 	<ul style="list-style-type: none"> • ASPIRIN (IB) • CLOPIDOGREL loading dose (IC) • ANTI IIbIIIa No age restriction <ol style="list-style-type: none"> a. Abciximab (IIaA) b. Eptifibatide (IIbB) c. Tirofiban (IIbC)
ANTIPLATELET CO-THERAPY FOR FIBRINOLYSIS	<ul style="list-style-type: none"> • ASPIRIN: No age restriction. Loading dose: 162- 325 mg orally; maintenance dose of 75-162 mg/daily (I A) • CLOPIDOGREL: <u>Age differences on loading dose</u> <ol style="list-style-type: none"> a. oral loading dose if age >75 years (IIaB) b. if age ≤75 years start with maintenance dose (IA) 	<ul style="list-style-type: none"> • ASPIRIN oral (soluble or chewable/non-enteric-coated) or i.v. dose of aspirin (IB) plus • CLOPIDOGREL: <u>Age differences on loading dose</u> <ol style="list-style-type: none"> a. oral loading dose if age ≤75 years (IB) b. if age >75 years start with maintenance dose (IIaB)
ANTITHROMBIN THERAPY	<ul style="list-style-type: none"> • Unfractionated Heparin: No age restriction. Weight adjustment • Enoxaparin: <u>Age adjustment</u> of bolus and maintenance dose • Bivalirudin: No age restriction. Reasonable choice for STEMI patients undergoing PCI who are at high risk of bleeding (IIaB) • Fondaparinux: No age restriction. Weight adjustment 	<ul style="list-style-type: none"> • Unfractionated Heparin: No age restriction. Weight adjustment • Enoxaparin: <u>Age adjustment</u> of bolus and maintenance dose • Bivalirudin: No age restriction. Reasonable choice for STEMI patients undergoing PCI who are at <u>high risk of bleeding</u> (IIaB) • Fondaparinux: No age restriction. Weight adjustment

Age considerations are underlined

PCI: percutaneous coronary intervention

REPERFUSION

Elegibility

General agreement exists that eligible STEMI patients who receive reperfusion (fibrinolytic therapy or percutaneous coronary intervention-PCI) have a lower risk of death than those who do not. The guidelines recommend considering time to presentation, time to PCI, and risk of STEMI, along with contraindications to treatment, when selecting reperfusion strategy; all of these factors are altered by age [39-41]. Numerous clinical trials have compared fibrinolytic regimens with each other [42-49] or have compared fibrinolytic regimens with direct PCI [43] [50-55]. Lack of consensus on reperfusion eligibility for AMI in the elderly includes lack of clinical trial data (frequent exclusion of patients ≥ 75 y), as well as comorbidity and delayed presentation [55, 56]. In addition, availability of reperfusion determines its selection, with fewer than half of elderly with STEMI (~40% of those ≥ 75 years of age) currently presenting to hospitals with PCI capability [57]. In the GRACE registry, 30% of STEMI patients presenting within 12 hours of symptoms did not receive therapy [58]. Factors associated with failure to receive reperfusion were similar to those associated with presentation delay: older age (≥ 75 years; odds ratio [OR], 2.63; 95% CI, 2.04 to 3.38), female sex, absence of chest pain, and congestive heart failure [58]. Many elderly STEMI patients also do not meet ideal criteria for reperfusion therapy for either PCI or fibrinolysis. Common reasons for excluding elderly from reperfusion are their delayed presentation (>6 hours from symptom onset) and ECG changes that are abnormal at baseline or of unclear duration [59]. Therefore, uncertain symptoms or ECGs at presentation, coexisting comorbid geriatric conditions, and patient preferences may contribute to observed treatment patterns in the elderly. The one best reperfusion strategy for elderly STEMI patients will likely remain undefined, but patient and treatment factors do determine its success.

Fibrinolytic therapy

Elderly patients are underrepresented in fibrinolytic trials because of explicit age inclusions, in addition to absence of inclusion criteria [42] [60-63]. For patients up to the age of 75 years, most trials showed that fibrinolytic therapy is associated with a survival

advantage similar to or greater than that seen in younger patients with STEMI. In older patients, the evidence concerning the risk/benefit ratio of thrombolysis treatment is less well established because the risk of related complications, particularly intracerebral hemorrhage (ICH), increases with age [64-67] and its efficacy may diminish [68]. Some studies have shown a survival advantage associated with the use of thrombolytic therapy in patients ≥ 75 years of age with AMI [69, 70], while others found an early mortality hazard [71-73], with a long term benefit in these patients [71].

Population-based studies have suggested that community-dwelling elderly patients over 75 years treated with thrombolytics have an increased risk of ICH of approximately 1.4 percent [74]. Features which confer higher risk include: age ≥ 75 years, female gender, black race, low body weight (<65 kg in women and <80 kg in men), prior stroke, systolic blood pressure >160 mmHg and administration of tissue plasminogen activator as compared with other agents [74]. The risk of cardiac rupture in patients receiving thrombolytic treatment is increased in patients older than 70 years and in women, with an incidence of 0.5 to 2 percent [75-77]. This risk does not appear to be related to the intensity of anticoagulation [76]. In a cohort of 706 patients ≥ 75 years included in the PRIMM75 study, thrombolysis was demonstrated as the strongest predictor of free wall rupture, with a three-fold increase within the first 48h of treatment compared with those who did not receive reperfusion therapy (OR 3.62; 95% CI 0.33-1.55) [78]. Thus, the increase in the incidence of free wall rupture is the most likely cause of the lack of benefit on early mortality associated with thrombolysis.

Despite increasing risks with fibrinolytic therapy in the elderly, adverse outcomes for untreated MI remain high. Therefore, the risk of ICH must be weighed against mortality risk [69] [79, 80]. Although the reperfusion therapy is favorable regardless of age, small sample size results in less certainty of benefit for those aged over 85 years. Two observational studies found that the benefit from thrombolytic therapy in younger patient groups did not extend to the extremes of age (>80 years and ≥ 85 years, respectively) [73] [77]. In a group of very elderly patients with STEMI (age ≥ 89 years) [81], those receiving thrombolytic therapy had a 44% mortality rate, largely owing to myocardial rupture. Hence, concerns persist in observational data that very elderly

patients may experience short-term adverse effects from thrombolytic therapy sufficient to counterbalance benefits. The ACC/AHA guidelines for management of myocardial infarction in 1999 recommended thrombolytic administration in patients younger than 75 years with acute ischemic symptoms associated with ST elevation or LBBB who present within 12 hours of symptom onset but with acknowledged disagreement on recommendations for patients with this presentation that are older than 75 years [82]. In contrast, the European guidelines [39],

and the updated AHA/ACC guidelines [40, 41] no longer classify thrombolytic therapy recommendations for ST elevation or LBBB within 12 hours of onset differently on the basis of patient age (previously class IA indication age <75, class IIa indication age ≥75) (Table 3). In conclusion, reperfusion therapy should always be considered if indicated, with careful attention to contraindications, patient's preferences and the special considerations of this age group (Figure2).

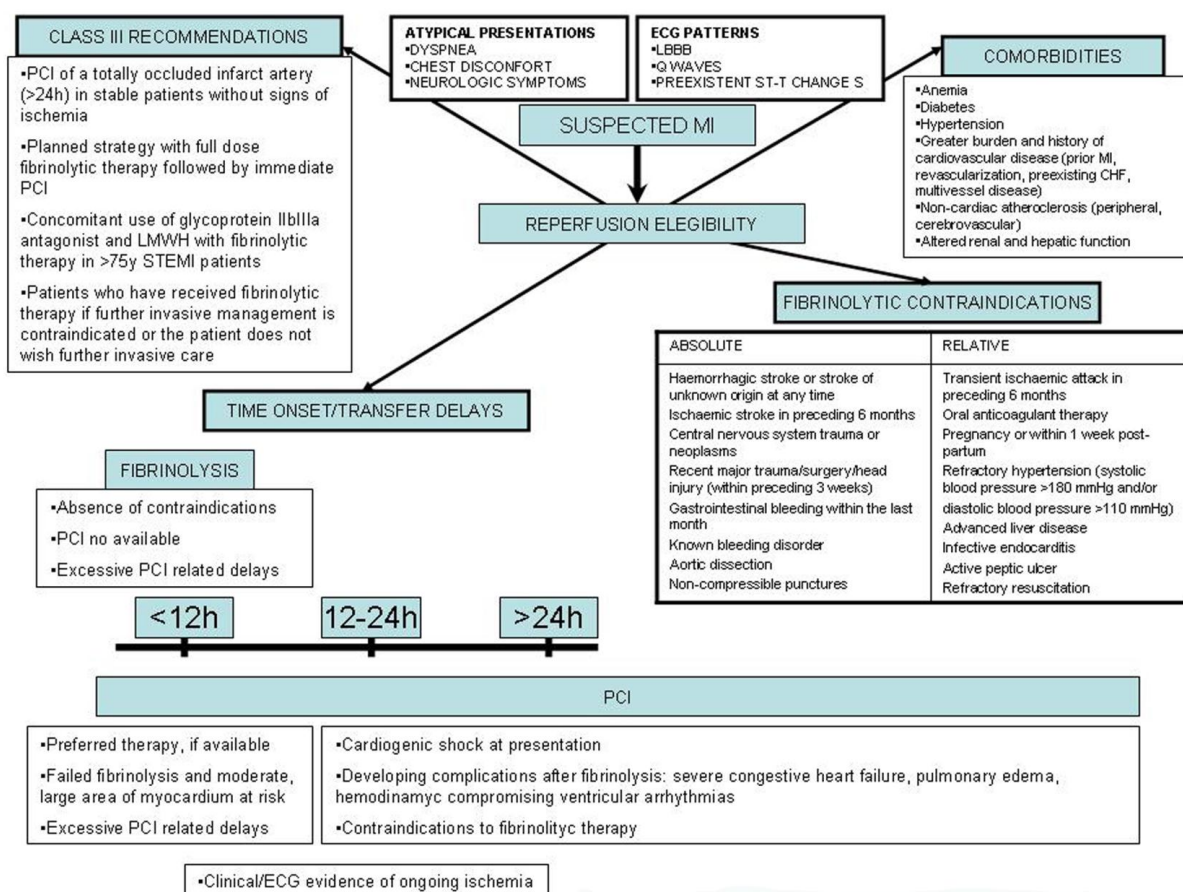


Figure 2: Determinants for reperfusion therapy decision. Reperfusion therapy should always be considered in the case of suspected MI. Time to presentation, transfer delays, specific fibrinolytic contraindications and comorbidities can balance the decision towards PCI over fibrinolytics. Class III recommendations or patient's preferences might justify the absence of reperfusion in selected cases.

PCI

Results from several studies and data base reviews suggest that primary angioplasty in experienced

centers is associated with improved outcomes compared with thrombolytic strategies in the elderly patients with STEMI [83-89]. Few small trials have been performed to specifically address the question of

Table 4: Reperfusion therapy studies. Age limits for inclusion are specified. Efficacy refers to primary endpoint

STUDY	AGE LIMITS	Primary endpoint	MEAN AGE	TREATMENT	EFFICACY		COMPLICATIONS			
							STROKE		BLEEDING	
Zijstra et al [51]	≤75 years	Recurrent ischemia before discharge	59±10	PTCA (n=70)	9%	p<0.001	0%	NS	3%	NS
			61±9	SK (n=72)	38%		3%		8%	
Ribeiro et al [85]	<75 years	Infarct related artery patency 48h postreated	57±10	PTCA (n=50)	74%	NS			0	NS
			55±10	SK (n=50)	80%				0	
Grinfield et al [86]	none	TIMI 3 flow infarct related artery pre-discharge		PTCA (n=54)	95%	P=0.01				
				SK (n=58)	63.6%					
Grines et al [50]	none	In hospital re-infarction	60±11	PTCA (n=195)	2.6%	P=0.06	0%	P=0.09	12.3%	NS
			60±11	t-PA (n=200)	6.5%		1.5%		8%	
Zijstra et al [87]	none	Death/nonfatal stroke/reinfarction at 6m	63±11	PTCA (n=47)	4%	P=0.02	2%	NS		
			59±12	SK (n=53)	20%		4%			
Ribichini et al [88]	<80	Reinfarction/rest angina prior discharge		PTCA (n=24)	4%	P=0.01				
				t-PA (n=26)	2.8%					
Garcia et al [89]	>18 years	In hospital death	63(53-70)	PTCA (n=109)	9%	P=0.02	0%	P=0.08	2.8%	NS
			60(53-74)	t-PA (n=111)	10.8%		2.7%		3.6%	
GUSTO IIb[43]	none 14.14%>75	Recurrent ischemia before discharge	59±10	PTCA (n=573)	9.6%	P=0.033	0.2% ^a	NS	40.3%	NS
			61±9	t-PA (n=565)	13.6%		0.9% ^a		34.2%	
Grines et al [91]	≥70years	Death or disabling stroke	78±6	PTCA (n=252)	11.3%	NS	0.8%	NS		
			77±6	Lytic (n=229)	13%		2.2%			
Goldberg et al [54]	≥70years	Composite of death, reinfarction, need for revascularization 6m	77±5	PTCA (n=44)	29%	P=0.001	2%	NS	0% ^b	P=0. 03
			76±5	t-PA (n=86)	93%		1%		17% ^b	
De Boer et al [90]	>75 years	Composite of death, reinfarction or stroke at 1y	80 (77-84)	PTCA (n=46)	20%	P=0.003	2.0%	P=0.34	11%	P=0.72
			81 (78-84)	SK (n=41)	44%		7.0%		7%	
Bardaji et al [93]	≥70years	In hospital mortality	81.5±4.6	No treat (n=172)	26.7%	NS	1.2%	P=0.06	2.9%	P=0.01
			79.8±4	Lytic (n=146)	21.2%		5.5%		6.8%	
			79.4±3.8	PTCA (n=92)	23.9%		2.2%		12%	

^a Percentage of disabling strokes^b Major bleeding

fibrinolytic therapy or PCI in elderly STEMI patients (Table 4). The first trial showed that patients >75 years treated with PCI had lower rates of death, MI, or stroke at 1 year (20% versus 44%; $P=0.003$) compared to streptokinase [90]. The mortality difference was not

a consistent finding across the studies [54], but PCI derived greater benefits both in terms of efficacy (lesser need for subsequent revascularization, reinfarction) and safety (lesser rates of stroke and bleeding) [54] [90-92]. However, PCI advantages

were confined to patients 70 to 80 years of age. Among those >80 years, there was no advantage of one strategy over the other [91]. A national registry that compared PCI, lytics and no reperfusion in AMI patients ≥ 75 years [93] found no mortality differences in this age group. However, excessive treatment delays and other deficiencies and inconsistencies in healthcare were highlighted, reinforcing the necessity for improving other measures than the reperfusion therapy itself. A recent multicenter study evaluated

the short and long term outcomes of nonagenarians with STEMI systematically treated with primary PCI [94]. Their results on in-hospital mortality rate (19%) and predictors for 6 month mortality (cardiogenic shock at presentation, TIMI flow after PCI and abciximab) suggested that selected nonagenarians with AMI might also benefit from successful primary angioplasty.

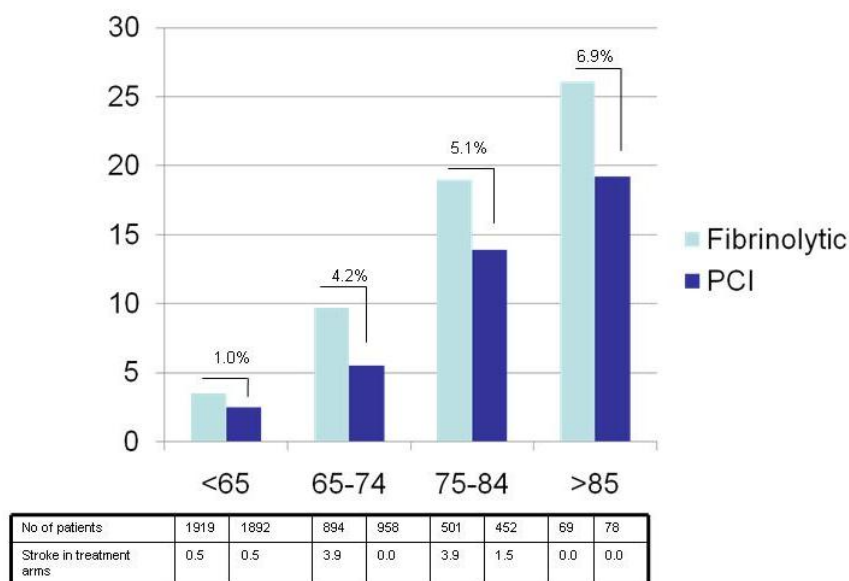


Figure 3: PCAT-2 collaborators [95]. Absolute mortality benefit of PCI with increasing age according to reperfusion strategies. The absolute mortality benefit increases from 1% at 65 years to 6.9% at ≥ 85 years of age. The number of patients includes with increasing age.

Pooled trials analyses can provide statistical confirmation of the mortality advantage with PCI in individual trials [83]. A review of 23 trials of PCI versus fibrinolytic therapy with longer follow-up (6 to 18 months) also found PCI to be superior for the reduction of death, reinfarction, stroke, and ICH [55]. The Primary Coronary Angioplasty Trialists' (PCAT) investigators pooled 11 randomized trials of PCI versus fibrinolytic therapy conducted from 1989 through 1996 ($n=2635$) [95]. In this analysis, PCI was favoured for reducing the 30-day mortality rate (13.3% versus 23.6%; $P<0.05$) among the elderly (≥ 70 years of age; $n=640$). The absolute mortality benefits of PCI were greater in high-risk patients, and the risk for hemorrhagic stroke was lower with PCI (relative risk=0.34; $P=0.009$). The PCAT-2 investigators expanded the analysis to include 22 randomized trials of PCI versus fibrinolytic therapy.

There was a benefit with PCI, particularly if the patient arrived 2 hours after symptom onset or if the patient was ≥ 65 years of age [96]. A subgroup analysis found that the absolute mortality advantage of PCI increased with age from 1% at 65 years to 6.9% at ≥ 85 years of age (Figure 3). Therefore, PCI is an effective strategy in preventing reinfarction and future revascularization. In the elderly, PCI is appealing because it can be applied in the absence of clear ST-segment elevation or chest pain and is effective despite hemodynamic status [40]. Two considerations deserve special consideration: the timing and availability of PCI, and cardiogenic shock at presentation.

Table 5. Considerations for selecting reperfusion therapy in the elderly

PCI	FIBRINOLYTICS	NO REPERFUSION
<ul style="list-style-type: none"> • Normal renal function • PCI can be performed without excessive delay (<1h) compared to fibrinolysis • Presentation >6h of symptom onset • Not known or suspected severe, diffuse vascular disease • Increased risk of ICH • Shock at presentation • Contraindications to fibrinolytic therapy • Absence ST elevation/pain 	<ul style="list-style-type: none"> • Diminished renal function • Delay to PCI would be excessive (>1h) compared to fibrinolysis • Can have the lytic within 2-3h from symptom onset 	<ul style="list-style-type: none"> • Too risky • Too late • Too small infarct (stable patient)
<i>Absolute benefits of PCI are greater in correlation to baseline risk</i>	<i>The greater benefit of fibrin specific agents may be offset by more ICH compared to SK</i>	

PCI: percutaneous coronary intervention. ICH: intracranial hemorrhage

The timing and availability of PCI often involve transfers. The Primary Angiography in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis-2 (PRAGUE-2) trial found no difference in death/MI with PCI or fibrinolytic therapy (streptokinase) if subjects were treated within 3 hours from symptom onset (7.4% versus 7.3%) [97]. The Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial shortened this interval to 2 hours and found that fibrinolytic therapy had a mortality advantage in this window (2.2% versus 5.7%; $P=0.058$) [98]. However, the Beyond 12 hours' Reperfusion AlternatiVe Evaluation (BRAVE-2) trial demonstrated that delayed PCI in STEMI patients who present >12 hours from symptom onset still reduced infarct size [99]. This is important because the elderly often present late and average delays to treatment are longer in practice settings than in clinical trials. The 2007 focused update [100] recommends rescue PCI, among others, in fibrinolytic treated STEMI patients meeting high risk criteria: cardiogenic shock, hemodynamic or electrical instability, persistent ischemic symptoms. These recommendations are based on the results of the REACT (Rescue

Angioplasty versus Conservative treatment or Repeat Thrombolysis) trial [101], which showed a clear benefit of rescue PCI (over repeated doses of fibrinolytics or medical management) in moderate to high risk patients who failed reperfusion, as well as meta-analysis of 8 rescue PCI trials (including REACT) [101-104]. Two recent trials have helped inform 2009 focused update [41]: the CARESS-in-AMI trial and the TRANSFER-in-AMI trial. CARESS-in-AMI studied only patients <75 years [105]. The percentage of patients ≥ 75 years in TRANSFER-in-AMI trial was 9.2%, and cardiogenic shock was an exclusion criteria [106]. Both studies found that high-risk STEMI patients treated at non-PCI hospitals improved outcomes when transferred immediately to a PCI facility rather than when medical therapy was continued with transfer for rescue PCI only if there was evidence of failed reperfusion. On the basis of this evidence, the guidelines now recommend that high risk patients who receive fibrinolytic therapy as primary reperfusion therapy at a non-PCI capable facility should be transferred as soon as possible to a PCI-capable facility where PCI can be performed. Consideration should be given to initiating a preparatory antithrombotic (anticoagulant plus antiplatelet)

regimen before and during patients transfer to catheterization laboratory (Class IIa, Level of Evidence B), and this is especially relevant in the elderly [39, 41, 100].

Table 6: Antiplatelet agents in elderly STEMI subgroups included in clinical trials

DRUG	STUDY	AGE LIMITS	ELDERLY n(%)	PRIMARY EFFICACY END POINT, ELDERLY		SIGNIFICANT BLEEDING OVERALL		SIGNIFICANT BLEEDING ELDERLY	
Clopidogrel	CLARITY [108]	18-75 years	Age >65y 1015 (29%)	Clop: 19%	NS	Clop: 1.9%	P=0.8	No increase in bleeding with clop by age	
				Plac: 23.1%		Plac: 1.7%			
	COMMIT [111]	none	Age ≥70y 11934 (26%)	Clop: 14.9%	NS ^a	Clop: 0.58%	P=0.59	Clop: 0.84%	P=0.48
				Plac: 16.2%		Plac: 0.55%		Plac: 0.72%	
Abciximab	GUSTO-V [47]	Age ≥18y	Age >75y 2237 (13%)	Abc: 18.3%	P=0.83	Abc: 4.6%	P<0.001	Abc ^b : 4.6%	NS
				No Abc: 17.9%		No Abc: 2.3%		No Abc ^b : 2.3%	
Ticagrelor (37.62% STEMI)	PLATO [115]	none	Age ≥75y 2878 (15%)	Ticag: 16.8%	NS	Ticag: 11.6%	P=0.43	Ticag: 14.2%	NS
				Clop: 18.3%		Clop: 11.2%		Clop: 13.3%	
Prasugrel (26% STEMI)	TRITON TIMI 38 [112]	Age ≥18y	Age ≥75y 1809 (13.29%)	Plas: 17.2%	NS	Plas: 2.4%	P=0.03	Plas: 4.3%	P=0.10 ^c
				Clop: 18.3%		Clop: 1.8%		Clop: 3.3%	

Clop: Clopidogrel. Plac: Placebo. Abc: Abciximab. Ticag: Ticagrelor. Pras: Prasugrel. NS: Non significant

^a Upper limit of the 95% CI < 1.0 for the relative risk of the primary end point with clopidogrel vs placebo

^b Intracranial bleeding

^c Was significant in the high risk bleeding group: .75y/prior stroke/60kg

The mortality rate for STEMI patients with shock is high regardless of reperfusion [107, 108]. According to the SHOCK study, a reduction in mortality at six months was observed either with angioplasty or bypass, but only in those aged under 75 years [107]. Although certain studies suggest a benefit on mortality after early revascularization in elderly patients selected according to individual criteria [109-111], current guidelines make a clear difference according to age. In the presence of cardiogenic shock, class I recommendation is given for patients <75 years, whereas in those ≥75 years the level of recommendation is II [100].

Taking all these data together, we may conclude that an invasive strategy is generally preferred. When a skilled PCI operator/team is available, and can perform the invasive procedure without delay (door to balloon time <90 minutes or within 1 hour of fibrinolytic administration), it is preferable to take the STEMI patient to the catheterization laboratory rather than administer fibrinolysis. Because of the increased risk of ICH with fibrinolysis with advanced age, the elderly patient is probably better treated with PCI, provided there is no excessive delay. As coronary thrombi mature over time, they become increasingly

resistant to fibrinolysis. Thus, PCI is the preferred reperfusion strategy if more than 3 hours have elapsed from the onset of symptoms, again assuming there is no significant delay in the anticipated time to balloon inflation. Finally, when the diagnosis is in doubt, an invasive strategy is clearly preferred; not only does it provide key diagnostic information regarding the patients' symptoms, but it also diminishes the risk of ICH associated with fibrinolysis (Figure 2/Table 5).

Ancillary antithrombotic therapy

The ideal adjunctive antithrombin therapy with reperfusion is of relevance to the elderly. It has been demonstrated that lower doses of **unfractionated heparin (UFH)** can reduce the rate of ICH associated with fibrinolytic therapy in the elderly [45] [112]. Subgroup analysis in the ASSENT-3 trial suggested similar benefits of **low-molecular-weight heparin** over weight-adjusted UFH in reducing the 30-day composite of death, in-hospital reinfarction, refractory ischemia, ICH, or major bleeding when given in combination with full-dose tenecteplase in patients with STEMI >75 years of age [46]. The high risk of ICH observed with enoxaparin in the ASSENT-3

PLUS [49] may relate to excessive dosing, unadjusted to a decreased creatinine clearance in the elderly. Dose reductions were successful in limiting enoxaparin-associated bleeding in The Enoxaparin Versus Unfractionated Heparin With Fibrinolysis for ST Elevation Myocardial Infarction (ExTRACT-TIMI- 25) [113, 114]. The Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS-6) trial studied **fondaparinux**, a newer agent that proved to be beneficial (reduced the rate of 30-day death or MI) in STEMI patients receiving fibrinolytic therapy or no reperfusion [115]. Among the older group of patients (≥ 62 years of age), fondaparinux demonstrated greater absolute risk reduction for the primary end point (2.7% versus 0.5%) along with a lower rate of bleeding [115]. The Hirulog and Early Reperfusion/Occlusion-2

investigators reported no difference in 30-day mortality in patients ≥ 65 years of age with STEMI treated with **bivalirudin** or weight-adjusted UFH as adjunct to streptokinase, but noted a trend toward lower in-hospital reinfarction in the bivalirudin-treated patients [48]. In The European ImproveR registry [116], bivalirudin effectively suppressed ischemic complications while maintaining a low rate of hemorrhagic consequences in several high-risk subgroups, including the elderly (age >65 years). Therefore, Bivalirudin represents an exciting alternative to UFH plus GP IIb/IIIa inhibitor in patients undergoing urgent and elective PCI with similar suppression of ischemic events, fewer bleeding complications, and the potential for greater cost savings and ease of administration [39-41].

Table 7. Strategies to prevent bleeding complications related to antithrombotic therapy in the elderly

ESTABLISHED STRATEGIES	POTENTIAL STRATEGIES
<ul style="list-style-type: none"> • Adjust dose of GP IIb/IIIa inhibitors, enoxaparin for patients with renal insufficiency • Consider bivalirudin use for PCI • Consider low dose Aspirin (81mg) for chronic antiplatelet therapy • Avoid triple anticoagulant therapy (Aspirin, clopidogrel, warfarin) when possible, including preferential use of bare metal stents to avoid long term and therapy during warfarin treatment 	<ul style="list-style-type: none"> • Reduce dose of chronic prasugrel, or preferential use of clopidogrel • Adjust doses of aspirin and clopidogrel based upon point-of-care platelet function assays • Assess for genetic polymorphisms to characterize potential response to long term thienopyridine use • PCI: use radial artery routinely versus femoral artery

GP IIb/IIIa inhibitors: glucoprotein IIb/IIIa inhibitors

PCI: percutaneous coronary intervention

The ideal adjunctive antiplatelet therapy is also of interest in this population (Table 6). Aspirin is recommended for routine administration to older patients with AMI [39-41]. The addition of **clopidogrel** to aspirin in STEMI patients was studied in 2 trials, one of which did not enroll any patients >75 years of age [114]. Patients aged 65-75 years ($n=1015$; 29%), however, showed that treatment with a loading dose of 300 mg of clopidogrel followed by a daily dose of 75 mg resulted in a 19 percent reduction in the odds of an occluded infarct related artery or death or recurrent MI by the time of angiography, without significant differences in bleeding rates when

compared to placebo [114]. The other study [117] found that clopidogrel without a loading dose in addition to aspirin was beneficial over placebo for reducing the rates of death, MI, or stroke in the overall population, but this was not significant in any subgroup, including those determined by age. There were increases in bleeding with dual antiplatelet regimens but no differing trend in risk as a function of older age [117]. The TRITON-TIMI 38 trial underscores the clinical significance of including elderly patients in ACS/PCI trials [118, 119]. The overall population derived a significant 19% relative risk reduction for the primary end point (30-day

Risk classification. PTCA collaborators [95]**Risk factors:**

- Anterior myocardial infarction
- Prior myocardial infarction
- Systolic blood pressure <115 mmHg
- Pulse rate >85 bpm

No Risk Factors	0	1	2	3	4
Age					
<50y	LOW RISK				
50-59y			INTERMEDIATE RISK		
60-69y					
≥70y	HIGH RISK				

Risk classification PRIMM75 model [138]. Multivariable analysis for 30-day mortality as compared to using predictors from the TIMI and GUSTO [9] models

Risk classification. PRIMM75 Model [35]		TIMI	GUSTO
Variable	OR (95% CI)	OR (95% CI)	OR (95% CI)
Killip Class			
•II	1.7 (0.9,3.2)	1.6 (0.8,3.0)	1.7 (0.9,3.2)
•III	1.3 (0.5,3.1)	1.6 (0.7,3.9)	1.8 (0.7,4.2)
•IV	16.1 (5.7,45.6)	20.5 (6.9,60)	20.4 (6.9,60)
Delay to admission >24h	3.5 (1.4,8.9)		
Age >75 (per year)	1.06 (1.01,1.12)	1.07 (1.02,1.13)	1.07 (1.02,1.13)
Heart rate (bpm)	1.02 (1.01,1.04)	1.03 (1.01,1.04)	1.03 (1.01,1.04)
Glucose level at admission (per mg/dl)	1.01 (1.00, 1.01)		
Hypercholesterolemia	0.5 (0.2, 0.9)		

Figure 4. Risk assessment in different score models

cardiovascular death, nonfatal MI, or nonfatal stroke) with **prasugrel** versus clopidogrel. Elderly patients (age ≥75years) constituted only 13% of the overall population. Their 6% relative risk reduction with prasugrel versus clopidogrel was nonsignificant, in contrast to the 25% relative risk reduction in younger patients. Current guidelines give prasugrel the same level of recommendation as clopidogrel for primary and nonprimary PCI, without age restrictions (Table 3) [100]. However, current prasugrel labeling recommends against its general use in patients ≥75years old [120]. Prasugrel has not been studied in patients who have received fibrinolytic therapy. Thus, for STEMI patients undergoing nonprimary PCI who received prior fibrinolytic therapy without a thienopyridine, only a loading dose with clopidogrel should be given as the thienopyridine of choice [100].

Few randomized studies have evaluated the benefit of **glycoprotein (GP) IIb/IIIa antagonists** in patients

over 75 years. Newer GP IIb/IIIa inhibitors appear efficacious in patients older than 70 years, although net benefit may decline with increasing age. In clinical trials, bleeding risk was increased about two fold with GP IIb/IIIa inhibitors, with the risk being about 2 percent [121]. Registry data confirmed this twofold greater risk in patients undergoing PCI who receive GP IIb/IIIa inhibitors compared with those who do not [122]. A review of the Food and Drug administration [123] found that deaths related to GP IIb/IIIa inhibitors treatment (mean age 69y) were associated with excessive bleeding, with ICH the most common site. The GUSTO-V [47], ASSENT-3 [46], and ASSENT-3 PLUS [49] trials also showed consistently higher ICH risk among elderly patients receiving half-dose fibrinolysis plus intravenous GP IIb/IIIa inhibitors versus fibrinolysis alone. Accordingly, the current ACC/AHA treatment guidelines recommend against GP IIb/IIIa inhibitors use in elderly patients

with STEMI receiving fibrinolysis [100]. Clinical trials assessing GP IIb/IIIa inhibitors in elderly PCI treated patients show conflicting results. Whereas in the Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up (ADMIRAL) Trial the observed benefit (reduction of death, reinfarction and urgent target vessel revascularization in total at 30 days and at 6 months) was higher in elderly than in younger patients [124], in the CADILLAC Trial abciximab use in elderly patients showed not net benefit but a slight increase of thrombocytopenia occurrence [125]. Importantly, in previous studies GP IIb/IIIa inhibitors during PCI in elderly patients was associated only with increased risk of minor bleeding complications, without excess of transfusions, and ICH rates [126]. A recent subanalysis of the elderly patients (≥ 65 years)

from the EUROTRANSFER (European Registry on Patients with ST-Elevation MI Transferred for Mechanical Reperfusion with a Special Focus on Upstream Use of Abciximab) [127] did not found higher risk of major bleeding, with comparable benefits to the younger group. Given the results of these studies it could be suggested that, in patients with STEMI, GP IIb/IIIa inhibitors may be used in primary angioplasty with coronary stenting [124], provided that contraindications have been ruled out (stroke, surgery or recent trauma, coagulation disorders, hepatic insufficiency, active hemorrhage, severe arterial hypertension), and after careful analysis of the trade-off between benefit and risks has been made [128]. Overall, it is important to consider specific measures to prevent bleeding complications in this population (Table 7).

Table 8. Factors contributing to the STEMI Age-Mortality relationship

Physiological aging of the heart	
<ul style="list-style-type: none"> • Decreased speed of myofibril contraction • Decreased length of contraction • Increased cardiac stiffness: diastolic dysfunction • Increased LV mass: Increased LVEDV, LVESV • Increased arterial stiffness: intimal medial thickness/dilation • Conduction system fibrosis and sinus node dysfunction • Decreased response to adrenergic stimulation (rate and contractility) • Altered vascular tone: endothelial dysfunction 	
Physiological aging of other systems	Other common comorbidities in the elderly
<ul style="list-style-type: none"> • Altered plasma volume distribution • Altered renal and hepatic function • Altered coagulation activity (\uparrowfactor VIII, fibrinogen) • Altered fibrinolytic activity (\uparrowplasmin/antiplasmin complex, D-dimer) • Inflammation (\uparrowhs-CRP, IL-6) • Deficient wound healing • Decreased pain sensing (ischemic) 	<ul style="list-style-type: none"> • Anemia • Diabetes • Hypertension • Greater burden and history of cardiovascular disease (prior MI, revascularization, preexisting CHF, multivessel disease) • Non-cardiac atherosclerosis (peripheral, cerebrovascular)

LV: left ventricular. LVEDV: left ventricular end-diastolic volume. LVESV: left ventricular end-systolic volume. MI: myocardial infarction. CHF: cardiac heart failure. hs-CRP: high sensitive C-reactive protein. IL-6: interleukin 6.

OUTCOMES

Mortality after STEMI increases exponentially with age [9] [37] [80] [129, 130]. In the GUSTO-I trial, the 30-day mortality rate increased 10-fold, from 3.0% among patients <65 years to 30.3% among those ≥ 85 years of age [37]. Total stroke and nonfatal disabling stroke increase more gradually with age and occur less

commonly than death, with overall rate of $<3\%$ among patients ≥ 85 years of age [9]. Observations from GRACE investigators showed that those patients aged 85 years or older with AMI had adjusted odds of death during the initial hospitalization more than 15 times greater than that of a patient under age 45 years [33]. The TRIANA registry found that elderly AMI patients treated in Spanish hospitals evolved

unfavorably during admission, with high incidence of mortality (24.1%) and complications [93]. Neither thrombolysis nor primary angioplasty improved 30-day mortality.

Although strokes are often fatal, death from other causes is still the most common adverse outcome in the elderly with STEMI. The high rate of death in the elderly corresponds to the frequent occurrence of electric and mechanical catastrophes, specifically free wall rupture and cardiogenic shock. These risks mirror age-related fundamental changes in cardiac anatomy [129] [131-133]: decreased vascular compliance, ventricular hypertrophy and remodeling, diastolic dysfunction and diminished response to adrenergic stimulation in the elderly (altered baroreceptor and β -receptor function lower heart rate and increase blood pressure during the acute event). Reduced lung and renal function make these organs prone to complications [129] [132] (Table 8). Heart failure and pulmonary edema, complications along this spectrum of adverse occurrences, occur in more than half of patients ≥ 75 years and 65% of patients ≥ 85 years of age [134]. Shock (hypotension with hypoperfusion) occurs in $>10\%$ of patients ≥ 75 years of age and is known to be due to ventricular or papillary muscle rupture or to advanced ventricular dysfunction [131] [135, 136]. In 706 elderly (age ≥ 75 years) STEMI patients, free wall rupture was more common in those treated with thrombolytic therapy (17.1%) than in either patients treated with PCI (4.9%) or who received no reperfusion (7.9%) [78]. Fibrinolytic therapy may have unique adverse myocardial effects in those of advanced age. Myocardial edema, contraction band necrosis, and intramyocardial hemorrhage are commonly noted at autopsy in elderly hearts after fibrinolysis [137]. The ability of STEMI treatments to improve outcomes in the very elderly, given their known physiological differences, is a question for future research. A subset of variables, most of them available at the moment of first medical attention, has recently shown their ability to adequately predict early mortality [138]. It led to the development and validation of a risk model especially calibrated for elderly patients, which could be proposed as complementary tool to choose the best approach in this population. Overall, this should be an individualized approach, aimed to provide the optimum outcome and most humanistic alternative in these relatively common and extremely lethal complications (Figure 2/Figure 4) [9][95][132] [138, 139].

CONCLUSION

The cardiovascular care of elderly STEMI patients should take place within the context of their multidimensional health status. Physicians should be aware of the atypical clinical presentations, as well as altered pharmacokinetics and the often altered cognitive and functional status of elderly patients. Up to 85 years of age, studies suggest a benefit associated with reperfusion strategies. The choice between fibrinolytics or PCI is determined by the presence or absence of cardiogenic shock, time from presentation, and comorbidity, which often tip the balance towards PCI in the elderly. The safety and efficacy of reperfusion, specifically fibrinolytic therapy, in the very elderly (≥ 85 years of age) are issues that require further investigation.

Abbreviations:

AMI: acute myocardial infarction; CAD:coronary artery disease; ECG: electrocardiographic; MI: myocardial infarction; ACS: acute coronary syndrome; STEMI: ST segment elevation MI; NRMI: National Registry of Myocardial infarction; LBBB: left bundle branch block; cTn: cardiac troponin; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; GRACE: Global Registry of Acute Coronary Events; PCI: percutaneous coronary intervention; ICH: intracerebral hemorrhage; PCAT: Primary Coronary Angioplasty Trialists; UFH: unfractionated heparin; GP: glycoprotein

References

- [1] Murray CJ, Lopez AD (1997). Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet*, 349:1269-1276.
- [2] Mathers CD, Bernard C, Iburg KM, Inoue M, Ma Fat D, Shibuya K, et al. Global burden of disease in 2002: data sources, methods and results. Geneva: World Health Organization; 2003 (GPE Discussion Paper No. 54)
- [3] The future of CVD. In: Mackay J, Mensah G, eds. *The Atlas of Heart Disease and Stroke*. Geneva, Switzerland: World Health Organization; 2004:74–75. Available at: http://www.who.int/cardiovascular_diseases/en/cvd_atlas_25_future.pdf. Accessed October 18, 2010.
- [4] Sugiura M, Hiraoka K, Ohkawa S (1976). Severity of coronary sclerosis in the aged: a pathological

- study in 968 consecutive autopsy cases. *Jpn Heart J*;17:471-478
- [5] Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, et al. (1999). Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. *Arterioscler Thromb Vasc Biol.*, 19(3):538-45.
 - [6] Kuller L, Borhani N, Furberg C, Gardin J, Manolio T, O'Leary D, et al. (1994). Prevalence of subclinical atherosclerosis and cardiovascular disease and association with risk factors in the Cardiovascular Health Study. *Am J Epidemiol.*, 139(12):1164-79.
 - [7] Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB (1998). Prediction of coronary heart disease using risk factor categories. *Circulation.*, 97(18):1837-47
 - [8] GRACE Investigators (2001). Rationale and design of the GRACE (Global Registry of Acute Coronary Events) project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J*, 141:190-9.
 - [9] Alexander KP, Roe MT, Chen AY, Lytle BL, Pollack CV Jr, Foody JM, et al. (2005). Evolution in cardiovascular care for elderly patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. *J Am Coll Cardiol*, 46:1479-87.
 - [10] Gurwitz JH, Col NF, Avorn J (1992). The exclusion of the elderly and women from clinical trials in acute myocardial infarction. *JAMA*, 268(11):1417-22.
 - [11] Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C (1999). Threats to applicability of randomised trials: exclusions and selective participation. *J Health Serv Res Policy*, 4:112-121
 - [12] Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, et al; GUSTO-I Investigators (1995). Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: results from an international trial of 41,021 patients. *Circulation*, 91:1659 -1668 .
 - [13] Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED (2001). Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *JAMA*, 286:708 -713
 - [14] Krumholz HM, Gross CP, Peterson ED, Barron HV, Radford MJ, Parsons LS, et al. (2003). Is there evidence of implicit exclusion criteria for elderly subjects in randomized trials? Evidence from the GUSTO-I Study. *Am Heart J*, 146:839-847.
 - [15] Melgarejo-Moreno A, Galcera-Tomas J, Garcia-Alberola A, Rodriguez-Garcia P, Gonzalez-Sanchez A (1999). Clinical and prognostic characteristics associated with age and gender in acute myocardial infarction: a multihospital perspective in the Murcia region of Spain. *Eur J Epidemiol*, 15:621-9
 - [16] Rittger H, et al. (2009). Influence of age on pain perception in acute myocardial ischemia: A possible cause for delayed treatment in elderly patients. *Int J Cardiol*, doi:10.1016/j.ijcard.2009.11.046
 - [17] Rogers WJ, Bowlby LJ, Chandra NC, French WJ, Gore JM, Lambrew CT, et al. (1994) Treatment of myocardial infarction in the United States (1990 to 1993). Observations from the National Registry of Myocardial Infarction. *Circulation*, 90(4):2103-14
 - [18] Milner KA, Vaccarino V, Arnold AL, Funk M, Goldberg RJ (2004). Gender and age differences in chief complaints of acute myocardial infarction (Worcester Heart Attack Study). *Am J Cardiol*, 93:606-608
 - [19] Aronow WS (1987). Prevalence of presenting symptoms of recognized acute myocardial infarction and of unrecognized healed myocardial infarction in elderly patients. *Am J Cardiol*, 60:1182
 - [20] Rogers WJ, Canto JG, Lambrew CT, Tiefenbrunn AJ, Kinkaid B, Shoultz DA, et al. (2000). Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the US from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2 and 3. *J Am Coll Cardiol*, 36(7):2056-63
 - [21] Sgarbossa EB, Wagner G (2007). Electrocardiography. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. 3 rd ed. Philadelphia: Lippincott-Raven, 978-1011
 - [22] Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction (2007). Universal definition of myocardial infarction. *Eur Heart J*, 28(20):2525-38
 - [23] Jeremias A, Gibson M (2005). Narrative review: alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. *Ann Intern Med*, 142:786 -791.
 - [24] Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, et al. Val-HeFT Investigators (2007). Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation*, 116:1242-1249.
 - [25] Schulz O, Paul-Walter C, Lehmann M, Abraham K, Berghöfer G, Schimke I, et al. (2007). Usefulness of detectable levels of troponin, below the 99th percentile of the normal range, as a clue to the presence of underlying coronary artery disease. *Am J Cardiol*, 100: 764-769.
 - [26] Zethelius B, Johnston N, Venge P (2006). Troponin I as a predictor of coronary heart disease and death in 70-year old apparently healthy men. *Circulation*, 113:1071-1078.

- [27] Eggers KM, Lind L, Ahlström H, Bjerner T, Ebeling Barbier C, Larsson A, et al. (2008). Prevalence and pathophysiological mechanisms of elevated cardiac troponin I levels in a population-based sample of elderly subjects. *Eur Heart J*, 29:2252–2258.
- [28] Eggers KM, Lind L, Venge P, Lindahl B. (2009). Will the universal definition of myocardial infarction criteria result in an overdiagnosis of myocardial infarction? *Am J Cardiol*;103(5):588-91.
- [29] Inbar R, Shoenfeld Y (2009). Elevated cardiac troponins: the ultimate marker for myocardial necrosis, but not without a differential diagnosis. *Isr Med Assoc J*, 11(1):50-3.
- [30] Yarzebski J, Goldberg RJ, Gore JM, Alpert JS (1994). Temporal trends and factors associated with extent of delay to hospital arrival in patients with acute myocardial infarction: the Worcester Heart Attack Study. *Am Heart J*, 128:255–263
- [31] Goldberg RJ, Yarzebski J, Lessard D, Gore JM (2000). Decade-long trends and factors associated with time to hospital presentation in patients with acute myocardial infarction: the Worcester Heart Attack Study. *Arch Intern Med*, 160:3217–3223
- [32] Gurwitz JH, McLaughlin TJ, Willison DJ, Guadagnoli E, Hauptman PJ, Gao X, et al. (1997). Delayed hospital presentation in patients who have had acute myocardial infarction. *Ann Intern Med*, 126: 593–599.
- [33] Avezum A, Makdisse M, Spencer F, Gore JM, Fox KA, Montalescot G, et al. (2005). Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J*, 149:67–73
- [34] Goldberg RJ, Steg PG, Sadiq I, Granger CB, Jackson EA, Budaj A, et al. (2002). Extent of, and factors associated with, delay to hospital presentation in patients with acute coronary disease (The GRACE Registry). *Am J Cardiol*, 89:791–796.
- [35] Saczynski JS, Yarzebski J, Lessard D, Spencer FA, Gurwitz JH, Gore JM, et al. (2008). Trends in prehospital delay in patients with acute myocardial infarction (from the Worcester Heart Attack Study). *Am J Cardiol* 102(12):1589-94.
- [36] Ottesen MM, Kober L, Jorgensen S, Torp-Pedersen C (1996). Determinants of delay between symptoms and hospital admission in 5978 patients with acute myocardial infarction. The TRACE Study Group. *Trandolapril Cardiac Evaluation*. *Eur Heart J*, 17:429–437.
- [37] White HD, Barbash GI, Califf RM, Simes RJ, Granger CB, Weaver WD, et al. (1996). Age and outcome with contemporary thrombolytic therapy: results from the GUSTO-I trial: Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries Trial. *Circulation*, 94: 1826–1833.
- [38] Newby LK, Rutsch WR, Califf RM, Simoons ML, Aylward PE, Armstrong PW, et al; GUSTO-1 Investigators (1996). Time from symptom onset to treatment and outcomes after thrombolytic therapy. *J Am Coll Cardiol*, 27:1646–1655
- [39] Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al; ESC Committee for Practice Guidelines (CPG) (2008). Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J*, 29(23):2909-45.
- [40] Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. (2004). ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: executive summary: a report of the ACC/AHA Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *J Am Coll Cardiol*, 44:671–719.
- [41] Kushner FG, Hand M, Smith SC Jr, King SB 3rd, Anderson JL, Antman EM, et al. (2009). 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*, 54(23):2205-41.
- [42] The GUSTO Investigators (1993). An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*, 329:673–682.
- [43] The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators (1997). A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med*, 336:1621–1628.
- [44] Cannon CP, Gibson CM, McCabe CH, Adgey AA, Schweiger MJ, Sequeira RF, et al; Thrombolysis in Myocardial Infarction (TIMI) 10B Investigators (1998). TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. *Circulation*, 98: 2805–2814.
- [45] Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators; Van De Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, Barbash G, et al (1999). Single-bolus

- tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomized trial. *Lancet*, 354:716-722.
- [46] Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators (2001). Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomized trial in acute myocardial infarction. *Lancet*, 358:605-613.
- [47] Topol EJ; GUSTO V Investigators (2001). Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet*, 357:1905-1914.
- [48] White H; Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators (2001). Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. *Lancet*, 358:1855-1863.
- [49] Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Arntz HR, et al. (2003). Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS Randomized Trial in Acute Myocardial Infarction. *Circulation*, 108:135-142.
- [50] Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, et al; the Primary Angioplasty in Myocardial Infarction Study Group (1993). A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med*, 328:673-679.
- [51] Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H (1993). A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med*, 328: 680-684.
- [52] Zijlstra F, Hoorntje JC, de Boer MJ, Reiffers S, Miedema K, Ottervanger JP, et al. (1999). Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med*, 341:1413-1419.
- [53] Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, et al; DANAMI-2 Investigators (2003). A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med*, 349:733-742.
- [54] Goldenberg I, Matetzky S, Halkin A, Roth A, Di Segni E, Freimark D, et al. (2003). Primary angioplasty with routine stenting compared with thrombolytic therapy in elderly patients with acute myocardial infarction. *Am Heart J*, 145:862-867.
- [55] Keeley EC, Boura JA, Grines CL (2003). Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*, 361:13-20.
- [56] Mehta RH, Granger CB, Alexander KP, Bossone E, White HD, Sketch H Jr (2005). Reperfusion strategies for acute myocardial infarction in the elderly: benefits and risks. *J Am Coll Cardiol*, 45:471-478.
- [57] Thiemann DR, Coresh J, Oetgen WH, Powe NR (1999). The association between hospital and survival after acute myocardial infarction in elderly patients. *N Engl J Med*, 340:1640-1648.
- [58] Eagle KA, Goodman SG, Avezum A, Budaj A, Sullivan CM, Lopez- Sendon J; GRACE Investigators (2002). Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). *Lancet*, 359:373-377.
- [59] Krumholz HM, Friesinger GC, Cook EF, Lee TH, Rouan GW, Goldman L (1994). Relationship of age with eligibility for thrombolytic therapy and mortality among patients with suspected acute myocardial infarction. *J Am Geriatr Soc*, 42:127-131.
- [60] Fibrinolytic Therapy Trialists' (FTT) Collaborative Group (1994). Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1,000 patients. *Lancet*, 343:311-322.
- [61] ISIS-2 (Second International Study of Infarct Survival) Collaborative Group (1988). Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet*, 2:349-360.
- [62] Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (1990). GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet*, 336:65-71.
- [63] Third International Study of Infarct Survival. Collaborative Group (1992). ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet*, 339:753-770.
- [64] Califf RM, Topol EJ, George BS, Boswick JM, Abbottsmith C, Sigmon KN, et al. (1988). Hemorrhagic complications associated with the use of intravenous tissue plasminogen activator in

- treatment of acute myocardial infarction. *Am J Med*, 85:354-359.
- [65] Anderson JL, Karagounis L, Allen A, Bradford MJ, Menlove RL, Pryor TA (1991). Older age and elevated blood pressure are risk factors for intracerebral hemorrhage after thrombolysis. *Am J Cardiol*, 68:166-170.
- [66] De Jaegere PP, Arnold AA, Balk AH, Simoons ML (1992). Intracranial hemorrhage in association with thrombolytic therapy: incidence and clinical predictive factors. *J Am Coll Cardiol*, 19:289-294.
- [67] Maggioni AP, Franzosi MG, Santoro E, White H, Van de Werf F, Tognoni G (1992). The risk of stroke in patients with acute myocardial infarction after thrombolytic and antithrombotic treatment. *N Engl J Med*, 327:1-6.
- [68] Lesnefsky EJ, Lundergan CF, Hodgson JM, Nair R, Reiner JS, Greenhouse SW, et al. (1996). Increased left ventricular dysfunction in elderly patients despite successful thrombolysis: the GUSTO-1 angiographic experience. *J Am Coll Cardiol*, 28:331-337.
- [69] White H (2000). Thrombolytic therapy in the elderly: weighing up the risks and benefits. *Lancet*, 356:2028-30.
- [70] Stenestrand U, Wallentin L; Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RISK-HIA) (2003). Fibrinolytic therapy in patients 75 years and older with ST-segment-elevation myocardial infarction. One-year follow-up of a large prospective cohort. *Arch Intern Med*, 163:965-971.
- [71] Berger AK, Radford MJ, Wang Y, Krumholz HM (2000). Thrombolytic therapy in older patients. *J Am Coll Cardiol*, 36(2):366-74.
- [72] Thiemann DR, Coresh J, Schulman SP, Gerstenblith G, Oetgen WJ, Powe NR (2000). Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. *Circulation*, 101(19):2239-46.
- [73] Soumerai SB, McLaughlin TJ, Ross-Degnan D, Christiansen CL, Gurwitz JH (2002). Effectiveness of thrombolytic therapy for acute myocardial infarction in the elderly: cause for concern in the old-old. *Arch Intern Med*, 162(5):561-8.
- [74] Brass LM, Lichtman JH, Wang Y, Gurwitz JH, Radford MJ, Krumholz HM (2000). Intracranial hemorrhage associated with thrombolytic therapy for elderly patients with acute myocardial infarction: results from the Cooperative Cardiovascular Project. *Stroke*, 31(8):1802-11.
- [75] Van de Werf F (2002). ASSENT-3: implications for future trial design and clinical practice. *Eur Heart J*, 23(12):911-2.
- [76] Becker RC, Hochman JS, Cannon CP, Spencer FA, Ball SP, Rizzo MJ, et al (1999). Fatal cardiac rupture among patients treated with thrombolytic agents and adjunctive thrombin antagonists: observations from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction 9 Study. *J Am Coll Cardiol*, 33(2):479-87.
- [77] Angeja BG, Rundle AC, Gurwitz JH, Gore JM, Barron HV (2001). Death or nonfatal stroke in patients with acute myocardial infarction treated with tissue plasminogen activator. Participants in the National Registry of Myocardial Infarction-2. *Am J Cardiol*, 87(5):627-30.
- [78] Bueno H, Martínez-Sellés M, Pérez-David E, López-Palop R (2005). Effect of thrombolytic therapy on the risk of cardiac rupture and mortality in older patients with first acute myocardial infarction. *Eur Heart J*, 26(17):1705-11.
- [79] Berger AK, Schulman KA, Gersh BJ, Pirzada S, Breall JA, Johnson AE, et al. (1999). Primary coronary angioplasty vs thrombolysis for the management of acute myocardial infarction in elderly patients. *JAMA*, 282(4):341-8.
- [80] Maggioni AP, Maseri A, Fresco C, Franzosi MG, Mauri F, Santoro E, et al. (1993). Age-related increase in mortality among patients with first myocardial infarctions treated with thrombolysis. The Investigators of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2). *N Engl J Med*, 329:1442-1448.
- [81] Martinez-Selles M, Datino T, Bueno H (2005). Influence of reperfusion therapy on prognosis in patients aged ≥ 89 years with acute myocardial infarction. *Am J Cardiol*, 95:1232-1234.
- [82] Ryan TJ, Antman EM, Brooks NH, Califf RM, Hillis LD, Hiratzka LF, et al (1999). 1999 update: ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction: Executive Summary and Recommendations: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation*, 100(9):1016-30.
- [83] Weaver WD, Simes RJ, Betriu A, Grines CL, Zijlstra F, Garcia E, et al. (1997). Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. *JAMA*, 278(23):2093-8.
- [84] Berger AK, Schulman KA, Gersh BJ, Pirzada S, Breall JA, Johnson AE, et al. (1999). Primary coronary angioplasty vs thrombolytics for the management of acute myocardial infarction in elderly patients. *JAMA*, 282:341-348.
- [85] Ribeiro EE, Silva LA, Carneiro R, D'Oliveira LG, Gasquez A, Amino JG, et al. (1993). Randomized trial of direct coronary angioplasty versus

- intravenous streptokinase in acute myocardial infarction. *J Am Coll Cardiol*, 22(2):376-80.
- [86] Grinfeld L, Berrocal D, Bellardi J, et al. Fibrinolytics versus primary angioplasty in acute myocardial infarction [abstract]. *J Am Coll Cardiol* 1996;27(Suppl):A222.
- [87] Zijlstra F, Beukema WP, van 't Hof AW, Liem A, Reijnders S, Hoorntje JC, et al. (1997). Randomized comparison of primary coronary angioplasty with thrombolytic therapy in low risk patients with acute myocardial infarction. *JACC*, 29:958-12
- [88] Ribichini F, Steffenino G, Dellavalle A, et al. Primary angioplasty versus thrombolysis in inferior acute myocardial infarction with anterior ST depression: a single-center randomized study [abstract]. *J Am Coll Cardiol* 1996;27:A221.
- [89] E García, J Elízaga, J Soriano.. (1997). Primary angioplasty versus thrombolysis with t-PA in the anterior myocardial infarction [abstract], *J Am Coll Cardiol*, 29:A-389
- [90] de Boer MJ, Ottervanger JP, van 't Hof AW, Hoorntje JC, Suryapranata H, Zijlstra F; Zwolle Myocardial Infarction Study Group (2002). Reperfusion therapy in elderly patients with acute myocardial infarction: a randomized comparison of primary angioplasty and thrombolytic therapy. *J Am Coll Cardiol*, 39(11):1723-8.
- [91] Grines C. Senior PAMI: a prospective randomized trial of primary angioplasty and thrombolytic therapy in elderly patients with acute myocardial infarction. *TCT 2005*; October 16–21, 2005; Washington DC.
- [92] Cequier A, Bueno H, Augé JM, Bardají A, Fernández-Ortiz A, Heras M (2005). Characteristics and mortality following primary percutaneous coronary intervention for acute myocardial infarction in Spain. Results from the TRIANA 1 (TRatamiento del Infarto Agudo de miocardio en Ancianos) Registry. *Rev Esp Cardiol*, 58(4):341-50.
- [93] Bardají A, Bueno H, Fernández-Ortiz A, Cequier A, Augé JM, Heras M (2005). Type of treatment and short-term outcome in elderly patients with acute myocardial infarction admitted to hospitals with a primary coronary angioplasty facility. The TRIANA (TRatamiento del Infarto Agudo de miocardio en Ancianos) Registry) *Rev Esp Cardiol*, 58(4):351-8
- [94] Danzi GB, Centola M, Pomidossi GA, Consonni D, De Matteis S, Stabile A, et al (2010). Usefulness of primary angioplasty in nonagenarians with acute myocardial infarction. *Am J Cardiol*, 106(6):770-3
- [95] Grines C, Patel A, Zijlstra F, Weaver WD, Granger C, Simes RJ; PCAT Collaborators; percutaneous transluminal coronary angioplasty (2003). Primary coronary angioplasty compared with intravenous thrombolytic therapy for acute myocardial infarction: six-month follow up and analysis of individual patient data from randomized trials. *Am Heart J*, 145: 47-57.
- [96] Boersma E; The Primary Coronary Angioplasty vs. Thrombolysis Group (2006). Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J*, 27:779-788.
- [97] Widimsky P, Budesinsky T, Vorac D, Groch L, Zelizko M, Aschermann M, et al; 'PRAGUE' Study Group Investigators (2003). Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction: final results of the randomized national multicentre trial-PRAGUE-2. *Eur Heart J*, 24:94-104.
- [98] Steg PG, Bonnefoy E, Chabaud S, Lapostolle F, Dubien PY, Cristofini P, et al; Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) Investigators (2003). Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation*, 108:2851-2856.
- [99] Schomig A, Mehilli J, Antoniucci D, Ndrepepa G, Markwardt C, Di Pede F, et al.; Beyond 12 Hours Reperfusion AlternatiVe Evaluation (BRAVE-2) Trial Investigators (2005). Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset: a randomized controlled trial. *JAMA*, 293:2865–2872.
- [100] Canadian Cardiovascular Society; American Academy of Family Physicians; American College of Cardiology; American Heart Association, Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, et al. (2008). 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*, 51(2):210-47.
- [101] Gershlick AH, Stephens-Lloyd A, Hughes S, Abrams KR, Stevens SE, Uren NG, et al. (2005). Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med*, 353:2758-68.
- [102] Alp NJ, Gershlick AH, Carver A, Stevens SE, Wilcox R (2008). Rescue angioplasty for failed thrombolysis in older patients: insights from the REACT trial. *Int J Cardiol*, 125:254-7.
- [103] Collet JP, Montalescot G, Le May M, Borentain M, Gershlick A (2006). Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy. *J Am Coll Cardiol*, 48:1326-35.

- [104] Wijeyesundera HC, Vijayaraghavan R, Nallamotheu BK, Foody JM, Krumholz HM, Phillips CO, et al. (2007). Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. *J Am Coll Cardiol*, 49:422-30.
- [105] Di Mario C, Dudek D, Piscione F, Mielecki W, Savonitto S, Murena E, et al. (2008). Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. *Lancet*, 371:559-68.
- [106] Cantor WJ, Fitchett D, Borgundvaag B, Ducas J, Heffernan M, Cohen EA, et al. (2009). Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med*, 360:2705-18.
- [107] Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, et al; SHOCK Investigators (1999). Early revascularization in acute myocardial infarction complicated by cardiogenic shock: should we emergently revascularize occluded coronaries for cardiogenic shock? *N Engl J Med*, 26:625-634.
- [108] Hochman JS, Buller CE, Sleeper LA, Boland J, Dzavik V, Sanborn TA, et al. (2000). Cardiogenic shock complicating acute myocardial infarction-etiology, management and outcome: a report from the SHOCK Trial Registry: SHould we emergently revascularize Occluded Coronaries for cardiogenic shock? *J Am Coll Cardiol*, 36(suppl A):1063-1070.
- [109] Dzavik V, Sleeper LA, Cocke TP, Moscucci M, Saucedo J, Hosat S, et al; SHOCK Investigators (2003). Early revascularization is associated with improved survival in elderly patients with acute myocardial infarction complicated by cardiogenic shock: a report from the SHOCK Trial Registry. *Eur Heart J*, 24:828-837.
- [110] Dauerman HL, Ryan TJ Jr, Piper WD, Kellett MA, Shubrooks SJ, Robb JF, et al. (2003). Outcomes of percutaneous coronary intervention among elderly patients in cardiogenic shock: a multicenter decade-long experience. *J Invasive Cardiol*, 15:380-384.
- [111] Dauerman HL, Goldberg RJ, Malinski M, Yarzebski J, Lessard D, Gore JM (2001). Outcomes and early revascularization for patients > or =65 years of age with cardiogenic shock. *Am J Cardiol*, 87:844-8.
- [112] Curtis JP, Alexander JH, Huang Y, Wallentin L, Verheugt FW, Armstrong PW, et al; ASSENT-2 and ASSENT-3 Investigators (2004). Efficacy and safety of two unfractionated heparin dosing strategies with tenecteplase in acute myocardial infarction (results from Assessment of the Safety and Efficacy of a New Thrombolytic Regimens 2 and 3). *Am J Cardiol*, 94:279-283.
- [113] Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, Sadowski Z, et al; ExTRACT-TIMI 25 Investigators (2006). Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med*, 354:1477-1488.
- [114] Sabatine MS, Cannon CP, Gibson CM, Lopez Sendon JL, Montalescot G, Theroux P, et al; CLARITY-TIMI 28 Investigators (2005). Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med*, 352:1179-1183.
- [115] Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al; OASIS-6 Trial Group (2006). Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 Randomized Trial. *JAMA*, 295: 1519-1530.
- [116] Madsen JK, Chevalier B, Darius H, Rutsch W, Wójcik J, Schneider S, et al. (2008). Ischaemic events and bleeding in patients undergoing percutaneous coronary intervention with concomitant bivalirudin treatment. *EuroIntervention*, 3(5):610-6.
- [117] Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, et al; COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group (2005). Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebocontrolled trial. *Lancet*, 366:1607-1621.
- [118] Wiviott SD, Antman EM, Gibson CM, Montalescot G, Riesmeyer J, Weerakkody G, et al. (2006). Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). *Am Heart J*, 152:627-35.
- [119] Wiviott SD, Braunwald E, McCabe CH, French PA, Smyth SS, Becker RC (2007). Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*, 357:2001-15.
- [120] US Food and Drug Administration (FDA). Cardiovascular and renal drug advisory committee briefing document on prasugrel for ACS. 2009. <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4412b1-01-FDA.pdf> (accessed 2 November 2010).
- [121] Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. (2009). Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*, 361:1045-57.
- [122] Horwitz PA, Berlin JA, Sauer WH, Laskey WK, Krone RJ, Kimmel SE; Registry Committee of the

- Society for Cardiac Angiography Interventions (2003). Bleeding risk of platelet glycoprotein IIb/IIIa receptor antagonists in broad-based practice (results from the Society for Cardiac Angiography and Interventions Registry). *Am J Cardiol*, 91(7):803-6.
- [123] Brown DL (2003). Deaths associated with platelet glycoprotein IIb/IIIa inhibitor treatment. *Heart*, 89(5):535-7.
- [124] Montalescot G, Barragan P, Wittenberg O, Ecollan P, Elhadad S, Villain P, et al. (2001). Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med*, 344:1895-903.
- [125] Prasad A, Stone GW, Aymong E, Zimetbaum PJ, McLaughlin M, Mehran R, et al. (2004). Impact of ST-segment resolution after primary angioplasty on outcomes after myocardial infarction in elderly patients: an analysis from the CADILLAC trial. *Am Heart J*, 147:669-75.
- [126] Sadeghi HM, Grines CL, Chandra HR, Dixon SR, Boura JA, Dukkipati S, et al. (2003). Percutaneous coronary interventions in octogenarians. glycoprotein IIb/IIIa receptor inhibitors' safety profile. *J Am Coll Cardiol*, 42:428-32.
- [127] Dziewierz A, Siudak Z, Rakowski T, Chyrchel M, Mielecki W, Janzon M, et al. (2010). Early abciximab administration before primary percutaneous coronary intervention improves clinical outcome in elderly patients transferred with ST-elevation myocardial infarction: data from the EUROTRANSFER registry. *Int J Cardiol*, 143(2):147-53.
- [128] Rich MW; PRICE-2 Organizing Committee; PRICE-2 Investigators (2003). Executive summary: Second Pivotal Research in Cardiovascular Syndromes in the Elderly (PRICE-2) symposium. Acute coronary syndromes in the elderly: mechanisms and management. *Am J Geriatr Cardiol*, 12(5):307-18, 327.
- [129] Goldberg RJ, Gore JM, Gurwitz JH, Alpert JS, Brady P, Strohsmittler W, et al. (1989). The impact of age on the incidence and prognosis of initial acute myocardial infarction: the Worcester Heart Attack Study. *Am Heart J*, 117:543-549.
- [130] Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, et al. (2000). Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation*, 101(22):2557-67.
- [131] Ornato JP, Peberdy MA, Tadler SC, Strobos NC. (2001). Factors associated with the occurrence of cardiac arrest during hospitalization for acute myocardial infarction in the Second National Registry of Myocardial Infarction in the US. *Resuscitation*, 48:117-123.
- [132] Burns TR, Klima M, Teasdale TA, Kasper K (1990). Morphometry of the aging heart. *Mod Pathol*, 3:336-342.
- [133] Nixon JV, Hallmark H, Page K, Raven PR, Mitchell JH (1985). Ventricular performance in human hearts aged 61 to 73 years. *Am J Cardiol*, 56:932-937.
- [134] Mehta RH, Rathore SS, Radford MJ, Wang Y, Wang Y, Krumholz HM (2001). Acute myocardial infarction in the elderly: differences by age. *J Am Coll Cardiol*, 38:736-741.
- [135] Thompson CR, Buller CE, Sleeper LA, Antonelli TA, Webb JG, Jaber WA, et al. (2000). Cardiogenic shock due to acute severe mitral regurgitation complicating acute myocardial infarction: a report from the SHOCK Trial Registry: Should we use emergently revascularize Occluded Coronaries in cardiogenic shock? *J Am Coll Cardiol*, 36(suppl A):1104-1109.
- [136] Menon V, Webb JG, Hillis LD, Sleeper LA, Abboud R, Dzavik V, et al. (2000). Outcome and profile of ventricular septal rupture with cardiogenic shock after myocardial infarction: a report from the SHOCK Trial Registry: Should we emergently revascularize Occluded Coronaries in cardiogenic shock? *J Am Coll Cardiol*, 36(suppl A):1110-1116.
- [137] Waller BF, Rothbaum DA, Pinkerton CA, Cowley MJ, Linnemeier TJ, Orr C, et al. (1987). Status of the myocardium and infarct-related coronary artery in 19 necropsy patients with acute recanalization using pharmacologic (streptokinase, r-tissue plasminogen activator), mechanical (percutaneous transluminal coronary angioplasty) or combined types of reperfusion therapy. *J Am Coll Cardiol*, 9:785-801.
- [138] Lenderink T, Hernández AV, Boersma E, Martínez-Sellés M, Juárez M, Sánchez PL, et al. (2010). Prediction of 30-day mortality in older patients with a first acute myocardial infarction. *Cardiology*, 115(1):1-9.
- [139] Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. (2000). TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation*; 102: 2031-2037.